In Pursuit of Precision Medicine in the Critically Ill

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Introduction

> For it is not enough to recognize that all our knowledge is, in a greater or less degree, uncertain and vague; it is necessary, at the same time, to learn to act upon the best hypothesis without dogmatically believing it (From 'Philosophy for Laymen' by Bertrand Russell).

Critical care medicine is, at present, a specialty of broad syndromes. This reflects the similarity in therapeutic approach required for the final common physiology that follows from many different pathological processes. Since their original definitions and descriptions, sepsis and acute respiratory distress syndrome (ARDS) are the two clinical conditions that have shaped health policy and dominated the research agenda in critical care [1, 2]. It is a truism to state that these are conglomerates of numerous different sub-syndromes; to make this observation is simply to restate the definition of sepsis and ARDS as common patterns arising from numerous different injuries. But it is also clear that, if we take the simple example of organ failure arising from a sterile versus an infectious insult, there is a very high likelihood that patients will respond differently to treatment with antibiotics. Or to take a more ambitious example, if we could diagnose, at presentation, the infectious agent caus-

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ing sepsis, we could then confidently treat with narrow spectrum antibiotics. In this way, sub-classifications of critical illness are almost certainly directly applicable to clinical practice.

With numerous statistically negative randomized controlled trials (RCTs) reported in both sepsis and ARDS, and strong conceptual arguments that patients presenting with these two conditions are heterogeneous, the idea of providing clinical care based on some patient level characteristic, along similar lines highlighted in cancer medicine is very appealing. Thus, critical care is contemplating approaches that are considered useful in cancer medicine and other clinical fields such as respiratory medicine, to inform clinical trials in sepsis and ARDS. However, the challenges with precision medicine in the critically ill could be related to the classic paper by Geoffrey Rose; "Sick Individuals and Sick Populations" [3]. The key principle is that individual and population approaches to improving health achieve different aims: the individual approach aims to protect susceptible (high-risk) patients, whereas the population approach aims to reduce the group level incidence of or outcome from diseases. In this short perspective, after discussing the rationale for current definitions, we discuss whether the heterogeneity and precision medicine concepts could inform future studies in sepsis and/or ARDS.

Rationale for ARDS and Sepsis Definitions with Predictive Validity

The latest ARDS [2] and sepsis definitions [1] and the corresponding clinical criteria [4–6] were derived to identify patient populations with predictive validity, by combining the consensus conference discussions with empirical evaluation of clinical data, resulting in valid and reliable critical illness syndromic definitions. ARDS is defined as acute onset hypoxemic respiratory failure despite a positive end-expiratory pressure (PEEP) of 5 cmH_2O or greater, with non-cardiogenic pulmonary edema evidenced by bilateral chest opacities. With this definition, stages of mild, moderate, and severe ARDS based on severity of hypoxemia, were associated with significantly higher mortality and increased median duration of mechanical ventilation in survivors [2]. Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, with organ dysfunction defined as an increase in the sequential organ failure assessment (SOFA) score of 2 points or more [4]. Septic shock was defined as a subset of sepsis in which profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone. Patients with septic shock can be clinically identified by a vasopressor requirement to maintain a mean arterial pressure (MAP) of 65 mmHg or greater and serum lactate level greater than 2 mmol/l in the absence of hypovolemia [5]. With this definition, sepsis and septic shock were associated with significantly higher mortality, compared to uncomplicated infection [1]. The predictive validity for mortality categories could potentially inform clinical care and trial design. For example, worsening ARDS severity has been aligned with treatment options, with severe ARDS aligned with need for neuromuscular blockade, prone position and extracorporeal support [6].

Heterogeneity

Heterogeneity is the interindividual variation in susceptibility to either the illness or the outcome from illness or both. When risk factors for the illness or outcome are reported, the unstated (and likely incorrect) assumption is that these risk factors confer similar risk to individuals in a population, which is often overlooked during design, conduct and interpretation of studies [7]. Variation in the risk of illness or outcome is generated either as a random phenomenon, or due to measurable differences in biological characteristics in patients [8, 9], resulting from genetic and/or environmental influences. It is challenging to discern the relative contribution of each of these influences on outcomes in a critically ill patient with ARDS or sepsis. For contextualization to ARDS and sepsis patients, heterogeneity could be categorized into patient, illness biology and treatment response level differences.

Patient-level Heterogeneity

Patient-level heterogeneity contemplates broadly two questions – (a) why did this patient get this disease at this time [3]?; and (b) why did this patient have a different outcome, compared to another patient who appeared similar in many aspects of illness? The answers to these questions rely on understanding the determinants of susceptibility amongst individuals to the illness (risk of illness) and the illness-related outcomes (risk of outcome). For example, as sepsis is infection-related organ dysfunction, the risk factors for sepsis would include risk factors for infection and risk factors for developing organ dysfunction in the context of infection. The risk factors for developing organ dysfunction in the context of infection are poorly understood. The risk factors for infection include age with an inverted parabolic distribution with highest risk at extremes of age; male sex; ethnicity with black race and Asians having a greater risk; and presence of one or more comorbidity [10].

Genetic predisposition to infectious diseases is strongly heritable [11, 12], presumably because of the strong selective pressure exerted by pathogens on our ancestors. Identifying – and understanding – the genetic factors underlying predisposition may lead directly to tractable therapeutic targets in the host [13]. Several strong associations with susceptibility to infections have been discovered (e.g., human immunodeficiency virus [HIV], West Nile virus [WNV], tuberculosis, malaria, influenza, meningococcus) [14–16], but these tend to be highly pathogen-specific. Whether there is general genetic susceptibility to sepsis, or even more broadly to a deleterious response to sterile injury, remains an open question. However, several lines of evidence suggest that responses to critical illness are likely to exhibit heritable variation in human populations. First, the consensus in critical care medicine, supported by many years of clinical and animal model research, is that organ failure seen during critical illness is complex, driven by immune-mediated injury and alterations in bioenergetics [17, 18], alongside individual predisposition discussed as patient heterogeneity. Second, immune phenotypes tend to be strongly heritable, and numerous genetic associations for both autoimmune and infectious

diseases have been discovered. Importantly, many of these disease associations are pleiotropic [19]. Hence, variation in the host responses to severe systemic injury is likely to be in part genetically-determined. Finally, and most directly, the results of the Genomic Advances in Sepsis (GAinS) and GenoSept studies have discovered some genetic associations with outcome in sepsis [20], which will be important candidates for further biological investigation.

Similarity within Sepsis and ARDS Biological Heterogeneity

Acute immune changes in sepsis, studied using whole blood transcriptomics, identifies a complex set of pro- and anti-inflammatory abnormalities in the innate and adaptive immune systems and alteration in genes highlighting mitochondrial dysfunction [21]. Antigen presenting cells, such as dendritic cells, monocyte-macrophage system, follicular dendritic cells, are impaired and there is accelerated depletion of B- and T-lymphocytes. When the same biology is studied by looking for unsupervised clustering algorithms, between 2 and 4 different sub-phenotypes within sepsis have been observed [18, 22–25]. At a clinical characteristic level, site of infection, numbers of organ dysfunctions, types of organ dysfunction and combination of organ dysfunctions also influence outcome from sepsis and add to this heterogeneity [26]. In ARDS, structural and functional disruption of the alveolar endothelial and epithelial barrier occur as a result of the generation of inflammasome and signalosome complexes, by leukocyte sensing of danger signals [27, 28]. The endothelial abnormalities and inflammatory responses observed in ARDS are also seen in sepsis and trauma [23, 29]. Furthermore, patients with ARDS could also be grouped into hyperinflammatory and non-reactive ARDS subphenotypes based on biomarkers and/or clinical variables [30–34] (Table 1).

Heterogeneity in Treatment Responses

For any treatment, the essential drivers arguing for a precision medicine approach, in the clinical or trial setting, include between-patient differences in treatment responses, patient-level interaction with treatment due to individual heterogeneity and the variation in treatment response determined by stage of illness due to variability in the lag time between onset of illness to treatment [35]. A simple example for the impact of time on treatment effect is the relationship between time to antibiotic treatment and outcome. In a cohort study, Seymour et al. highlighted that in patients who had the 3-hour Surviving Sepsis Campaign Bundle (blood culture, antibiotic therapy and measurement of lactate) completed within a 12-hour period, every extra hour taken to complete the bundle was associated with a significant increase in mortality [36]. Similarly, the treatment effect of drugs has been shown to vary with illness severity, using activated protein C trials in sepsis and effect of PEEP in ARDS [37] as examples. A related concept in this context is heterogeneity in treatment response, which is a crude omnibus test for differences in responses to

Table 1 Recent studies describing acute respiratory distress syndrome (ARDS) and sepsis sub-phenotypes

First author [reference] (population)	Sub-phenotypes	Comment
Calfee [33] (ARDS)	Hyperinflammatory phenotype versus phenotype-1	Latent class analysis-based grouping based on clinical and biomarker data. The discriminant markers between phenotypes were IL-6, sTNFR1, vasopressor use, IL-8, bicarbonate
Famous [32] (ARDS)	Hyperinflammatory phenotype versus pPhenotype-1	Latent class analysis-based grouping based on clinical and biomarker data. The discriminant markers between phenotypes were IL-8, sTNFR1, vasopressor use, bicarbonate, minute ventilation
Bos [30] (ARDS)	Reactive phenotype versus uninflamed phenotype	Agglomerative hierarchical cluster analyses based only on biomarker data. The discriminant markers between phenotypes were IL-6, IFNγ, ANG1/2, PAI-1
Davenport [23] (Sepsis)	Sepsis response signature-1 versus sepsis response signature-2	Agglomerative hierarchical clustering based on Ward's method using pan-leukocyte transcriptome using microarray. The discriminant markers between two phenotypes were seven genes – *DYRK2*, *CCNB1IP1*, *TDRD9, ZAP70*, *ARL14EP*, *MDC1*, and *ADGRE3*
Scicluna [25] (Sepsis)	Four molecular endotypes named as Mars1 to Mars4	Agglomerative hierarchical clustering based on Ward's method using pan-leukocyte transcriptome using microarray. The study showed that a 140-gene expression signature reliably stratified patients with sepsis to the four endotypes. The study also reported biomarkers for each endotype to facilitate clinical use: Mars1 = BPGM and TAP2; Mars2 = GADD45A and PCGF5; Mars3 = AHNAK and PDCD10; Mars4 = IFIT5, NOP53

IL: interleukin; *sTNFR1*: soluble tumor necrosis factor receptor; *IFNγ*: interferon gamma; *ANG1/2*: angiotensin; *PAI-1*: plasminogen activator inhibitor-1; *DYRK2*: dual specificity tyrosine phosphorylation regulated kinase 2; *CCNB1IP1*: cyclin B1 interacting protein 1; *TDRD9*: tudor domain containing 9; *ZAP70*: zeta chain of T-cell receptor associated protein kinase 70; *ARL14EP*: ADP ribosylation factor like GTPase 14 effector protein; *MDC1*: mediator of DNA damage checkpoint 1; *ADGRE3*: adhesion G protein-coupled receptor; *E3BPGM*: bisphosphoglycerate mutase; *TAP2*: ATP binding cassette subfamily B member transporter 2; *GADD45A*: growth arrest and DNA damage inducible alpha; *PCGF5*: polycomb group ring finger 5; *AHNAK*: AHNAK nucleoprotein; *PDCD10*: programmed cell death 10; *NOP53*: ribosome biogenesis factor

treatment and illness-related outcomes arising from all factors contributing to heterogeneity and stochasticity of risk. This has been illustrated using simulation of sepsis and ARDS RCTs [38] and by using completed RCT data from intravenous immunoglobulin trials in sepsis [39]. As the risk of death changes in a trial population, the differences in mortality between the intervention arm and the usual arm also changes. This could potentially highlight a risk of outcome-specific subgroups within ARDS and sepsis who are likely to benefit the most from the intervention.

Stratified Medicine and Enrichment

Stratified medicine refers to identifying groups of patients based on either characteristics of disease or likely treatment response at a population level. Enrichment markers are biomarkers that help identify treatment responders and/or patients with higher risk of certain outcomes [40]. Thus, in the context of sepsis and ARDS, stratified medicine (enrichment) of clinical trial populations is a potentially viable strategy, as differential biological mechanisms and the technical ability to prospectively identify patient subsets exist. For example, in children with septic shock, using a 100-gene profile and serum protein biomarkers, it is possible to identify two patient subsets, with different outcomes, and differential responses to corticosteroid treatment [41]. Similarly, in adults with septic shock, corticosteroid responders can be identified using a three-biomarker panel [42]. Similarly, ARDS subsets, which respond differently to ventilator and fluid management, have been identified using data from completed ARDS trials [32, 33].

In 2007, Trusheim et al. [40] proposed three necessary conditions required for effective stratified medicine for a disease: (a) differential biological mechanisms; (b) multiple treatment options; and (c) a clinical biomarker that links patient subsets to treatment responses. Sadly, in critical care medicine, we are a long way from meeting the second criterion: multiple treatment options.

However, as efforts have progressed to achieve these goals, both in critical care medicine and beyond, it has become clear that a necessary first step is the identification of a pattern, or subgroup, within heterogeneous patient populations. In itself, this is purely an exercise of academic interest, but where a common biological mechanism can be found, there is a reasonable chance that some current or future therapy might have a different effect in patients belonging to a given subgroup – this essentially is the definition of a disease endotype [43]. The process of identifying endotypes is conceptually identical to the approach taken by our medical forebears: a syndrome becomes a disease when the underlying mechanism is thought to be known. Given the interplay of multiple mechanisms, two or more endotypes are likely in ARDS and sepsis.

The identification of a disease endotype has immediate clinical relevance, since it is likely that patients with a given endotype will respond differently to some therapies when compared with patients having other patterns of disease. Once an endotype is convincingly discovered, considerable academic and commercial investment is applied to identifying treatments and viable biomarkers with which to make the diagnosis [44]. It is therefore important to consider carefully what criteria must be met for this enterprise to proceed. Differential response to therapy is probably too high a bar in critical care medicine, because in many cases the fundamental problem is that we lack specific diseases and therapies for those diseases. Thus, a major aspiration of this field is that, by better understanding the underlying biology, we may be able to create or repurpose drug treatments to modulate the host response to injury. At present, however, efforts to achieve this goal have failed. Aside from heterogeneity, this is not necessarily because of lack of understanding of the molecular mechanisms involved, but due to the complex interplay of many

mechanisms contributing to the final outcome; targeting one particular mechanism may not yield the desired treatment benefit. Progress in identifying distinct disease processes in critical illness should not be held back by this limitation.

We therefore propose the following, permissive criteria to conclude that valid and reliable endotypes exist in critically ill populations. Subgroups should be:

1. Consistency
2. Biological plausibility
3. Clinical plausibility
4. Feasibility of implementation in clinical care and/or trials

Consistency can be measured using standard criteria for generalizability to other populations of similar patients. Where, as is often the case, expensive new technologies have been used to observe patterns in a group of patients, consistency must necessarily be determined within the original population, using a bootstrapping approach or similar.

Plausibility is a vague and subjective concept but we contend that most investigators know it when they see it. Biological plausibility can – in some cases – be determined by statistical tests applied to the biological signature that defines membership of a subgroup. Such signatures may depend on systematic collections of known biology, for example for pathway enrichment, or genome-wide methods [45], such as co-expression module enrichment [46]. If the number of tests performed is faithfully reported, these approaches can provide convincing evidence that a given grouping is biologically real. Clinical plausibility is an extension of this concept. Biological plausibility has obvious limitations: there are many real subgroupings of any population of patients. Hence, if there is not a predictable mechanism by which a given subgrouping could turn out to have a differential treatment effect, or at least a differential effect on prognosis, then the risk of failure is expected to be high.

Finally, feasibility represents a compromise between the truth of detection (validity) and reliability of measurements to identify subgroups. For example, a cytokine profile for identifying corticosteroid responders in septic shock [42] could be considered to have greater feasibility compared to a 100-gene expression panel [41], but with different reliability and validity. Importantly, it is possible, but not necessary, for clinical outcome to be different between endotypes: patients with different diagnoses can have identical statistical probabilities for a given outcome. A focus on outcome runs the risk of detecting severity markers, rather than distinct biological processes.

Precision Medicine

Fundamentally, precision medicine represents a scenario where detecting one or more biological abnormalities in patients helps pair them to treatment(s), based on the individuals' favorable treatment response–adverse effect profiles. Most precision medicine advances have been in oncology, although consistent success is lim-

ited. For example, super-responders to everolimus treatment considered as exemplar for precision oncology [47] have not been consistently replicated. Furthermore, the cancer-free survival amongst patients with relapse and/or refractory tumors is not impressive and super-responders to targeted chemotherapy may be a much smaller cancer population than previously considered [48]. For example, a recently published phase II multicenter RCT enrolled 741 adult patients with any kind of metastatic solid tumour refractory to standard of care. From this population, 40% of patients had at least one molecular alteration that matched with one of the 10 treatment regimens and 195 patients were randomized to receive experimental treatment specific for pathway mutations or standard of care. There were no differences in efficacy or adverse event endpoints between the intervention and control arms [49]. These lessons from precision oncology approaches must be seriously considered [50], when testing precision medicine in critically ill patients with heterogeneous syndromes such as sepsis or ARDS.

Conclusion

ARDS and sepsis often occur in older patients with comorbidity, resulting in critical illness. Heritable characteristics and environmental factors influence the incidence and outcomes from ARDS and sepsis. We have begun to group ARDS and sepsis patients with similar biological characteristics and consider stratified or precision medicine as the solution for overcoming statistically negative clinical trials. Key biological and clinical plausibility challenges need to be addressed to achieve major breakthroughs in future trials and in the clinical care of sepsis and ARDS patients.

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